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Jefferson T, Demicheli V, Pratt M

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[Intervention Review]

Vaccines for preventing plague

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ABSTRACT

Background

Plague is endemic in China, Mongolia, Burma, Vietnam, Indonesia, India, large parts of Southern Africa, the United States and South America. There are three types of vaccines (live attenuated, killed and F1 fraction) with varying means of administration.

Objectives

The objective of this review was to assess the effects of vaccines to prevent plague.

Search methods

We searched MEDLINE (1966 to February 2011), EMBASE (1985 to February 2011), CENTRAL (*The Cochrane Library* 2011, Issue 2) and reference lists of articles. We handsearched the journal 'Vaccine' (up to 1997) and contacted experts in the field.

Selection criteria

Randomized trials comparing live and killed plague vaccines against no intervention, placebo, other plague vaccines or vaccines against other disease (control vaccines).

Data collection and analysis

Three reviewers assessed the eligibility of trials.

Main results

No trials were included.

Authors' conclusions

There is not enough evidence to evaluate the effectiveness of any plague vaccine, or the relative effectiveness between vaccines and their tolerability. Circumstantial data from observational studies suggest that killed types may be more effective and have fewer adverse effects than attenuated types of vaccine. No evidence appears to exist on the long-term effects of any plague vaccine.

23 April 2019

No update planned

Other

We are aware that new vaccines are under development and will revisit in April 2020 whether a review update will be useful.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing plague

Plague is a rare disease now, but can be life threatening. It is transmitted by fleas and related to rat infestation. There are different forms of the disease, but they can all lead to blood poisoning and to death, although antibiotics are effective against the bacterium that causes it. Vaccines are available for use in laboratory staff working on the disease; however when the authors searched the literature they found no studies of sufficient quality to be included in this review. We therefore cannot make confident decisions about the effectiveness or tolerability of any plague vaccines.

BACKGROUND

The disease

Plague is a serious life threatening bacterial disease, caused by the bacterium *Yersinia pestis*. Both bubonic plague (infected lumps under the skin), and pneumonic plague can lead to septicaemia (blood poisoning) and death.

The disease is transmitted by flea bites, usually from the rat, and has a short incubation period (1 to 7 days). The reservoir of infection is the Black Rat (Rattus), small rodents and other animals. Although untreated plague has a high mortality rate, *Y. pestis* remains highly sensitive to antibiotic action. Apart from the great epidemics of history, which have made plague a famous disease, in this century plague activity has consisted of focal, sporadic disease with a variable distribution of carriers. Outbreaks of the disease have been confined to the developing world (Mozambique, Peru, India, Zaire) and are associated with deprivation, overcrowding and low standards of housing where rats and vectors can proliferate. Plague is endemic in China, Mongolia, Burma, Vietnam, Indonesia, India, large parts of Southern Africa, the United States and South America (Gage 1996).

Vaccines

Yersin produced the first vaccine in 1896 using horse serum from animals immunised with plague bacilli. There are three contemporary producers of plague vaccines known to us:

1. Aerosol vaccines (from former USSR State manufacturers)

This is a live avirulent EV76 strain vaccine, produced in many centres in the former USSR, which has been in use since 1908, has apparently recently been used for mass immunisation of large parts of the Indian population, is theoretically thought to be capable of reverting to full virulence after administration. Assessment of effectiveness of both human vaccines is fraught with ethical and practical difficulties. For example live attenuated vaccines are thought to be less effective but have a lower incidence of side effects. However we were unable to locate a summary of evidence of such issues. EV76 can be administered as an aerosol or subcutaneously.

2. Formalin inactivated vaccines (Greer Laboratories Inc, North Carolina).

The Greer vaccine (USP) (formerly produced by Cutter Biological Ltd in the USA) is a formalin-inactivated vaccine which is thought to confer protection against bubonic but not pneumonic plague for several months after injection. Production of the vaccine has been bedevilled by the relatively high production cost, the need for protection of operators, and its reportedly high systemic side-effects (in one series, 30% of vaccinees) (Marshall 1974). Overall effectiveness assessment of this vaccine is based on observations such as the one carried out by Cavanaugh and colleagues in US troops deployed during the Vietnam war. Between 1961 and 1971 eight cases were diagnosed among vaccinated US troops (a rate of one case per 1,000,000 man-years of exposure) whereas the equivalent rate for the unvaccinated Vietnamese population was estimated as 333 (Cavanaugh 1974). The Greer vaccine costs $150 for a 20ml bottle (sufficient for fourteen first courses and two boosters) and is administered with three intramuscular injections (0, 3 and 9 months). This amounts to a cost of $10.72 per person vaccinated. The company have produced unpublished data, from a collaborative study with the US military, that their present vaccine has no different immunogenic or reactogenic properties, as measured by the Mouse Potency Index (MPI), from the original Cutter product.

3. Heat killed organisms (CSL Ltd, Victoria Australia).

The CSL vaccine which costs £8 for a 0.5 ml vial is made up of a suspension of heat-killed organisms of *Y. pestis* in saline with phenol used as an antiseptic (CSL 1992). The vaccine is administered subcutaneously in three doses at 1-4 week intervals. Booster doses are necessary every six months.

There are at present no candidates for a synthetic vaccine, although there are several reasons why a new vaccine should be developed. These include a reputedly high level of side-effects and short-lived immunity and apparent lack of protection against pneumonic plague by current vaccines (Perry 1997). Additionally no review of the experimental evidence of the effects of plague vaccines exists, and their role in controlling outbreaks of the disease in endemic countries is unclear.

Summary of observational data

We searched MEDLINE (1966-96) and EMBASE (1985-96) on plague and vaccine in a retrieval strategy identical to the "search strategy for identification of studies" except we did not restrict it to randomised comparisons. All studies identified were observational, and there were no comparators or the comparators were not clear. As none of these studies met the inclusion criteria, we have summarised the findings they report in the following paragraph. Information about each individual study is contained in the excluded trials section of this review.

The excluded studies deal with aspects of the efficiency and safety of different vaccines (live attenuated, freeze-dried, and F1 fraction). Means of administration vary from oral to nebulised, subcutaneous and intramuscular. The F1 fraction vaccine appears to have low efficacy (below 60%) and high systemic side-effects (35% of vaccinees). The attenuated vaccine given through the oral route appears to have similar lack of efficacy (Vorob'ev). Live attenuated vaccines delivered by aerosol have low efficacy and low side-effects, while if delivered by intramuscular or intradermal administration they appear to have efficacy of between 82 to 90% but a high increase of local (38-98%) and systemic (38.4-90%) side-effects. Killed vaccines appear to have the best combination between efficacy (86%) and side-effects. Local side-effects range between 29 and 50% with short term systemic side-effects of up to 20% incidence. Given the non-randomized, uncontrolled and unblinded nature of the data, however, no firm conclusions can be drawn. The only controlled cohort study we identified (Otten 2), dating from the 1930s, indicates high effectiveness of the attenuated vaccine in preventing intra-epidemic mortality.

OBJECTIVES

To assess the effectiveness and safety of vaccines against human plague in relation to antibody titres, side-effects and disease incidence from controlled clinical trials.

The following hypotheses will be tested:

- There is no difference in the number of cases of plague taking place in a placebo/control group compared with the intervention group.
- There is no difference in the number and severity of side-effects (both systemic and localised) occurring in the vaccine and control groups.

METHODS

Criteria for considering studies for this review

Types of studies

Any prospective randomized or quasi-randomized studies comparing plague vaccines in humans with placebo, control vaccines or no intervention. Comparisons of different schedules or doses of the vaccine are included.

Types of participants

Well adults or children irrespective of immune status or special risk category. The latter is defined as persons exposed to plague accidentally or during an epidemic.

Types of interventions

Live or killed vaccines or fractions thereof, administered by any route.

Types of outcome measures

Immunologic: rise in antibody titre (regardless of length of follow-up). Specifically: seroconversion at six and twelve months after primary vaccination.

Adverse: number and seriousness of side-effects (classified as local and systemic). Systemic side-effects will include cases of malaise, nausea, fever, arthralgias, rash, headache and more generalised and serious signs. Local side-effects will comprise induration, soreness and redness at the site of inoculation.

Clinical: numbers of cases avoided by vaccination. Specifically: incidence of plague in the intervention and non-intervention groups. A case will be defined clinically and the denominator will be person-months of potential exposure. In trials were exposure is not recorded, the number of cases divided by the number vaccinated/not vaccinated in the defined geographical study area will be compared.

Search methods for identification of studies

We carried out an electronic search of MEDLINE using the extended search strategy of the IDG with the following search terms or combined sets from 1966 to February 2009 in any language: plague; vaccine (live); and vaccine (killed).

We carried out a search of EMBASE (1985 to September 2011), and Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 2, 2011). Additionally, we handsearched the journal Vaccine from its first issue to the end of 1997. Randomized Controlled Trials (RCTs) and Clinical Controlled Trials (CCTs) retrieved were loaded on to the Vaccines Field and Cochrane Library databases of trials. We also read the bibliography of retrieved articles in order to identify further trials.

In order to locate unpublished trials we wrote to the following: manufacturers; researchers active in the field; and the first or corresponding authors of studies evaluated (but not necessarily included) in the review.

Data collection and analysis

Selection by reviewers. All retrieved studies were read.

RESULTS

Description of studies

We identified and retrieved 20 studies which could have possibly fitted our inclusion criteria. However, after the text was read, reviewers agreed that none fitted the entry criteria (see Characteristics of excluded studies for individual study descriptions). Additional analysis considering all studies as observational was equally not possible because of the lack of clear comparators in all studies.

Risk of bias in included studies

No assessment was carried out due to a lack of studies which met the entry criteria.

Effects of interventions

As there were no trials that met our inclusion criteria, we turn in our discussion and recommendations for research section to the observational studies described in the background section to highlight research questions that future trials could address.

DISCUSSION

The lack of trial evidence, or at least of good observational evidence, on the effects of plague vaccine is disconcerting, given the burden of the disease in endemic countries. Additionally, the evidence we have collected is of apparent low quality, judged by today's standards. The highly variable quality of the reports makes interpretation of their content very difficult.

In general, there seems to be reasonable circumstantial evidence that killed and attenuated vaccines afford protection against bubonic plague, but at the cost of frequent short-term side-effects, especially in the case of the latter vaccine. In general cutaneously administered vaccines appear to have a higher incidence of side-effects than their nebulised counterparts but are considerably more effective. Long term side-effects remain unknown. It is difficult to assess the effectiveness of the vaccines in protecting against morbidity and mortality given the high reliance on serological changes as an outcome and the certain widespread presence of confounders and biases in the studies. Serological changes are the first basic level of evidence, however, we believe that properly designed, conducted and reported trials of plague vaccines are now overdue and our review highlights this necessity.

Both the Greer and CSL vaccines are expensive and apparently available in small quantities, limiting their use in epidemic circumstances. Overall, the use of such vaccines in potentially exposed populations will depend on circumstances, but on the basis of the current evidence it is difficult to formulate firm conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

Confident decisions on effectiveness of any plague vaccine, relative effectiveness between vaccines, and tolerability cannot be made based on reliable evidence.

Circumstantial data from observational studies suggest that killed types maybe more effective and have fewer side-effects than attenuated types, and this requires additional research. No evidence appears to exist on the long-term side-effects of all types of plague vaccines.

Implications for research

Plague is a disease of low incidence and high mortality with a social stigma image and supposed military importance which in the past has led to lack of collaboration and publication of studies. Thus there are three principal themes for research:

Firstly, there is an urgent requirement for well-designed field evaluation of current vaccines, especially the killed version which may be safer. Ideally a new vaccine should also be developed, perhaps using recombinant technology, which could address the problems of side-effects as well as the pneumonic variant of the disease; but a drive to achieve this should not inhibit proper evaluation of existing licensed products. The following questions may be worth testing or exploring when designing the trial:

- Are the high levels of local and systemic side-effects with attenuated vaccines borne out in randomised comparisons?
- Do attenuated vaccines given by aerosol have low immunogenicity?
- Are killed vaccines more immunogenic than attenuated vaccines?
- Do killed vaccines have fewer side-effects than attenuated vaccines?

Secondly, field evaluation faces several hurdles whether it is examining present or emerging vaccines. Probably the first methodological step in designing further trials is to have consensus on outcome measures so that comparisons could be facilitated between trials. Although not fully validated, the Mouse Potency Index could be one such measure together with surveillance outcomes (such as the reduction in cases and deaths). Additionally, each available vaccine (predominantly the killed or inactivated Y. pestis) and possibly those that are not commonly used (e.g.Tjiwidej attenuated strain) should be subject to the same outcome measures to allow comparisons. The process of trial design should also take into consideration the need for prevention in outbreaks and therefore incorporate an abbreviated vaccine schedule in its protocol.

Thirdly, central coordination is needed to achieve comparable outcome measures, thus international collaboration is the key feature of future plague vaccine endeavours. It is likely that leadership would come from a significant stake holder, such as the military, and could involve those countries where plague is endemic with a recent history of epidemics.

ACKNOWLEDGEMENTS

The reviewers would like to thank Dr Tim Brooks, Mrs Carol Hobbs, Mr William White Jr and Mrs Judy Dance for help received.

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Aleksandrov 2 *{published data only}*

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Reisman RE. Allergic reactions due to Plague vaccine. *Journal of Allergy* 1970 Jul;**46**(1):49-55.

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Perry 1997

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aleksandrov 1	METHODS: - Design: experimental, non-randomised comparison - Comparison(s): aerosol vs subcutaneous/cutaneous vs cutaneous administration - Outcome(s): full blood count (presence or absence of leucocytosis) and presence of adverse reactions - Follow-up duration: 6 months (for full blood count one week) PARTICIPANTS: - Setting: Former USSR - Study population: 534 healthy persons aged 18-25 (aerosol route), 100 healthy persons aged 18-25 (subcutaneous/cutaneous route), 5600 healthy males aged 18-25 (cutaneous route) - At risk groups: not known - Incidence of plague in study population: not known INTERVENTIONS: - Type of vaccine(s): Live EB vaccine - Route: aerosol immunisation in room, subcutaneous, cutaneous only - Schedule: four immunisation sessions - Dose: 10-12 grams dispersed in 112 cubic metres. OUTCOMES: - Stated conclusions: aerosol appears the safest route - Estimates of efficacy: incidence of side-effects - Estimates of safety: no clinical adverse reactions reported to the aerosol route while 98 (98%) of vaccinees in the subcutaneous arm had local reactions with 90 reporting systemic reactions. In the cutaneous administration arm, 3.8% (216/5600) persons had systemic reactions of different severity. NOTES: (Internal validity) - Selection bias: issue not addressed - Information bias: issue not addressed - Confounding: issue not addressed

Study	Reason for exclusion
	(External validity) - Inference from study to whole population - Precision: issue not addressed - Appropriateness of statistical methods: not stated - quality of reporting: poor REASON(S) FOR EXCLUSION Study is a non-randomised experiment with cohorts of grossly unequal numbers. No efforts has been made to minimise bias in selection and blinding allocation.
Aleksandrov 2	METHODS: - Design: experimental - Comparison(s): response to brucellosis, tularemia, anthrax and plague vaccines - Outcome(s): incidence of side-effects and agglutination of sera - Follow-up duration: 10 days PARTICIPANTS: - Study population: 78 healthy volunteers - At risk groups: not known - Incidence of plague in study population: not known - Setting: former USSR in 1957-58 INTERVENTIONS: - Type of vaccine(s): 1,17 and EV strains - Route: aerosol - Schedule: 5-15 minutes exposure to aerosol in sealed room - Dosage: 100-150 million microbes (concentration not specified) OUTCOMES: - Stated conclusions: aerosol vaccine is mildly reactogenic and safe - Estimates of efficacy: 30 of the 78 vaccinees had complement fixation. After 30-45 days this declined (no numbers given). - Estimates of safety: 5/78 had pyrexia NOTES: (Internal validity) - Selection bias: issue not addressed - Information bias: issue not addressed - Confounding: issue not addressed (External validity) - Inference from study to whole population - Precision: issue not addressed - Appropriateness of statistical methods: issue not addressed - quality of reporting: below average REASON(S) FOR EXCLUSION Non-randomised comparison with population numbers which are difficult to work out. The effect of biases is impossible to assess.
Bartelloni	METHODS: - Design: cohort without controls - Comparison(s): none - Outcome(s): antibody titre rise and incidence of side-effects - Follow-up duration: 390 days PARTICIPANTS: - Study population: 29 healthy male volunteers aged 18-25 - At risk groups: not specified - Incidence of plague in study population: not specified INTERVENTIONS: - Type of vaccine(s): plague vaccine USP (Cutter Laboratories California) - Route: IM (deltoid region)

Study	Reason for exclusion
	- Schedule: 0 (1.0ml), 90 (0.2ml) 270 (0.2ml) OUTCOMES: - Stated conclusions: 25/29 (86%) subjects produced indirect haemagglutination antibodies by day 30. During the length of follow-up, antibodies decreased. Booster intervention produced an immediate response in 26 subjects (90%). Table 1 in the study reports incidence of side-effects. No systemic reactions were observed, local reaction were: on day 25/29, on day 90 21/29 and on day 270 16/29. - Estimates of efficacy: not given - Estimates of safety: not given NOTES: (Internal validity) - Selection bias: no measures taken to minimise - Information bias: no measures taken to minimise - Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: impossible to assess - Appropriateness of statistical methods: not relevant - quality of reporting: impossible to assess REASON(S) FOR EXCLUSION Non-randomised comparison. The effect of bias is impossible to assess.
Ganochko	METHODS: - Design: immunised cohort study. Unclear presence of controls. - Comparison(s): simultaneous immunisation with three different vaccines vs ? controls - Outcome(s): seroconversion, Antibody rise and side-effects - Follow-up duration: 30 days with 7 days hospitalisation for observation of a sub-cohort of 50 participants PARTICIPANTS: - Study population: 1930 healthy volunteers aged 18-21 and ? controls - At risk groups: none mentioned - Incidence of plague in study population: not relevant as participants are healthy volunteers INTERVENTIONS: - Type of vaccines: dried live plague vaccine - ChV- (Central Asiatic Institute of Pestilential Infections), adsorbed typhoid fever vaccine - BTV- (Tashkent Scientific Research Institute of Vaccines and Sera) and dried petechial typhus vaccine - STV - (Scientific Research Institute of the Academy of Medical Sciences of the former USSR). - Route: SC with needleless injector. All three vaccines administered in same site. - Schedule: 1 ml OUTCOMES: - Stated conclusions: BTV+STV+ChV stimulated antibody formation to all vaccine components while causing acceptable (to the authors) side-effects. - Estimates of efficacy: Antibody rise and seroconversion rates are similar to monovalent vaccine responses in ? historical cohorts (Table 4) - Estimates of safety: At 12 hours post-inoculation 38.8% of vaccinees had slight (temperature 37.1-37.5 C) reactions and 1.8% medium (temperature 37.6-38.5 C) reactions. Most reactions did not last longer than 2 days. Controls had no reactions NOTES: (Internal validity) - Selection bias: no measures taken to minimise - Information bias: no measures taken to minimise - Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: impossible to assess - Appropriateness of statistical methods: not used

Study	Reason for exclusion
	- Quality of reporting: not good but may have lost in translation REASON(S) FOR EXCLUSION Non-randomised comparison. Unclear use of controls
Grasset 1	METHODS: - Design: Non-randomised, non-comparative population study - Comparison(s): None - Outcome(s): Side-effects; Cases of plague in vaccinated population - Follow-up duration: Study conducted between 1941-44 PARTICIPANTS: - Study population: Natives and Europeans living in regions of South Africa that endured plague epidemics - At risk groups: Study conducted in areas undergoing plague epidemics - Incidence of plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): Avirulent strains (EV and South African) of Y. pestis - Route: Subcutaneous - Schedule: One dose of 1 cc (1000 million organisms) for those over 12 years old. 5-12 years of age given 0.5 cc; and under 5 years of age given 0.25 cc OUTCOMES: - Stated conclusions: Single live avirulent plague inoculation (1,000 million organisms) with usual anti-plague measures, realises a safe, easily applicable, well accepted and efficient mass plague control method. - Estimates of efficacy: Limited number of plague cases, a total of fifteen cases with seven deaths, observed among 24000 persons immunised during nine of the plague outbreaks - Estimates of safety: Very mild type of vaccinal reaction observed. In male adults local reaction was limited to 4.2% and moderate general reaction to 3.7% NOTES: (Internal validity) - Selection bias: no measures taken to minimise - Information bias: no measures taken to minimise - Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: no measures taken to estimate - Appropriateness of statistical methods: not applicable - Quality of reporting: average REASON(S) FOR EXCLUSION Non-randomised, non-comparative population study
Grasset 2	METHODS: - Design: Description of attenuated vaccines immunisation campaigns and their effect on several bubonic and pneumonic plague outbreaks in the 1930s in South Africa. - Comparison(s): not given - Outcome(s): decrease of incidence rate by 82% - Follow-up duration: not known PARTICIPANTS: - Study population: bushmen and their families and population of the Orange Free State. - At risk groups: populations subject to epidemics - Incidence of plague in study population: not known INTERVENTIONS: - Type of vaccine(s): live attenuated Tjiwidej strain - Route: subcutaneous

Study	Reason for exclusion
	- Schedule: not specified OUTCOMES: - Stated conclusions: efficacious and safe vaccine - Estimates of efficacy: 82% - Estimates of safety: not quantified. "Highly safe" vaccine NOTES: (Internal validity) - Selection bias: issue not addressed - Information bias issue not addressed - Confounding issue not addressed (External validity) - Inference from study to whole population - Precision: issue not addressed - Appropriateness of statistical methods: issue not addressed - Quality of reporting: fair REASON(S) FOR EXCLUSION Non-randomised uncontrolled descriptive study
Kozlov	—
Marshall 1	—
Marshall 2	METHODS: - Design: Retrospective testing of plague vaccine recipients' sera - Comparison(s): None - Outcome(s): Antibody titre rise and the incidence of local and systemic reactions - Follow-up duration: None PARTICIPANTS: - Study population: 117 individuals for whom complete samples of serum were available, 30 of whom included because of a history of local and systemic reactions to plague vaccine - At risk groups: Not stated - Incidence of Plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): plague vaccine USP (Cutter Laboratories, California) - Route: IM - Schedule: Primary series of 0, 2 and 4 weeks. Booster dose every six months. Recipients received between 10 and 51 inoculations OUTCOMES: - Stated conclusions: Administration of multiple inoculations of plague vaccine resulted in establishment of stable levels of antibody titres for 92% of 117 individuals - Estimates of efficacy: See stated conclusions - Estimates of safety: Not stated NOTES: (Internal validity) - Selection bias: no measures taken to minimise - Information bias: no measures taken to minimise - Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: no measures taken to estimate - Appropriateness of statistical methods: not relevant - quality of reporting: good REASON(S) FOR EXCLUSION

Study	Reason for exclusion
	Retrospective, non-randomised, study of sera taken from recipients of plague vaccine over a twenty year period
Medinskii	METHODS: - Design: Case report of severe reaction to plague vaccine - Comparison(s): None - Outcome(s): Side effects observed - Follow-up duration: 21 days PARTICIPANTS: - Study population: Single person - At risk groups: Not stated - Incidence of plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): Live plague vaccine - Route: Intradermal - Schedule: Not stated OUTCOMES: - Stated conclusions: Personnel organising prophylactic mass-vaccinations should anticipate the possibility of such severe allergic reactions. - Estimates of efficacy: Not stated - Estimates of safety: Patient underwent a severe allergic reaction NOTES: (Internal validity) - Selection bias: not addressed - Information bias: not addressed - Confounding: not addressed (External validity) - Inference from study to whole population - Precision: not addressed - Appropriateness of statistical methods: not addressed - quality of reporting: fair REASON(S) FOR EXCLUSION Non-randomised, non-comparative, case report of an allergic reaction to plague vaccine in one person
Meyer 1	METHODS: - Design: No prospective study or trial - Comparison(s): Not relevant - Outcome(s): Not relevant - Follow up duration: Not relevant PARTICIPANTS: - Study population: Not relevant - At risk groups: Not relevant - Incidence of Plague in study population: Not relevant INTERVENTIONS: - Type of vaccine(s): Not relevant - Route: Not relevant - Schedule: Not relevant OUTCOMES: - Stated conclusions: Not relevant - Estimates of efficacy: Not relevant - Estimates of safety: Not relevant NOTES:

Study	Reason for exclusion
	(Internal validity) - Selection bias: Not relevant - Information bias: Not relevant - Confounding: Not relevant (External validity) - Inference from study to whole population - Precision: Not relevant - Appropriateness of statistical methods: Not relevant - Quality of reporting: Not relevant REASON(S) FOR EXCLUSION No prospective study or trial. This paper is a 'history' of plague vaccine reporting work completed by others
Meyer 2	METHODS: - Design: Non-randomised comparison - Comparison(s): Avirulent strains 1122 and EV76 compared - Outcome(s): Clinical and serological reactions - Follow up duration: Sera tested on day 21 PARTICIPANTS: - Study population: Human volunteers - At risk groups: Not stated - Incidence of plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): Avirulent strains 1122 and EV76 - Route: Subcutaneous - Schedule: One dose - Dose: Not stated OUTCOMES: - Stated conclusions: As a whole, the immunogenic response to the various plague preparations expressed as MPI (see note) was disappointingly slight - Estimates of efficacy: Not stated - Estimates of safety: 2 cases of severe lymphangitis, 6 very mild local reactions, and 8 severe local reactions in 92 participants (conclusions based on this data not given) NOTES: (Internal validity) - Selection bias: no measures taken to minimise - Information bias: no measures taken to minimise - Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: no measures taken to estimate - Appropriateness of statistical methods: not relevant - quality of reporting: poor REASON(S) FOR EXCLUSION Poorly and briefly reported non-randomised comparison of two strains of the same plague vaccine Note: The Mouse Protection Index (MPI) is an often quoted serological outcome measure. It is calculated by dividing the percentage of mortality among test mice by the average day of death. Thus, the lower the index the higher the level of protection; in general MPI equal to or smaller than 10 is considered to correlate to clinical protection (Gage et al, 1996)
Meyer 3	METHODS: - Design: No prospective study or trial - Comparison(s): Not relevant - Outcome(s): Not relevant - Follow up duration: Not relevant

Study	Reason for exclusion
	PARTICIPANTS: - Study population: Not relevant - At risk groups: Not relevant - Incidence of plague in study population: Not relevant INTERVENTIONS: - Type of vaccine(s): Not relevant - Route: Not relevant - Schedule: Not relevant OUTCOMES: - Stated conclusions: Not relevant - Estimates of efficacy: Not relevant - Estimates of safety: Not relevant NOTES: (Internal validity) - Selection bias: Not relevant - Information bias: Not relevant - Confounding: Not relevant (External validity) - Inference from study to whole population - Precision: Not relevant - Appropriateness of statistical methods: Not relevant - Quality of reporting: Not relevant REASON(S) FOR EXCLUSION No prospective study or trial. This paper is a 'history' of plague vaccine reporting work completed by others
Meyer 4	METHODS: - Design: Non-randomised comparison - Comparison(s): Compares four vaccines (Army plague vaccine, fraction I antigen, avirulent vaccine strains 1122 and Tjiwidej) - Outcome(s): Appearance of protective antibodies (according to the MPI) - Follow-up duration: 28 days after last inoculation PARTICIPANTS: - Study population: Human volunteers - At risk groups: Not stated - Incidence of plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): Army plague vaccine, fraction I antigen, avirulent vaccine strains 1122 and Tjiwidej - Route: Not stated - Schedule: Army plague vaccine and fraction I antigen - 3 doses; Avirulent vaccine strains 1122 and Tjiwidej - 1 dose - Dose: Army plague vaccine - 7 billion plague bacilli (all three doses); fraction I antigen - 2.5 mgm (all three doses); avirulent strain 1122 and Tjiwidej - 1000 million plague bacilli (one dose) OUTCOMES: - Stated conclusions: Administration of purified fraction I plague antigen to non-immune human volunteers results in the production of large quantities of protective antibodies in the blood. Formalin-killed virulent plague bacilli and one strain (No. 1122) of living avirulent bacilli are decidedly less effective. The well-known strain "Tjiwidej" as used in these studies proved non-immunogenic - Estimates of efficacy: Not stated - Estimates of safety: Not stated NOTES: (Internal validity) - Selection bias: no measures taken to minimise

Study	Reason for exclusion
	- Information bias: no measures taken to minimise - Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: no measures taken to estimate - Appropriateness of statistical methods: not relevant - quality of reporting: poor REASON(S) FOR EXCLUSION A poorly reported non-randomised comparison
Meyer 5	METHODS: - Design: Experimental, non-randomised comparison - Comparison(s): Compared varied doses; addition of typhoid vaccine or alum to regimen - Outcome(s): Local and general reactions observed; MPI; antibody titre rise - Follow up duration: 128 days PARTICIPANTS: - Study population: Duty personnel at the Letterman Army Hospital - Group I: 31 subjects; Group II: 25 subjects; Inmates of San Quentin Prison - Group III: 10 subjects; Group IV: 7 subjects; Group V: 25 subjects; Group VI: 25 subjects - At risk groups: Not stated - Incidence of plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): Fraction I antigen - Route: Letterman Army Hospital - subcutaneous; revaccination was intracutaneous, subcutaneous or intramuscular. San Quentin Prison - subcutaneous, intracutaneous or intramuscular - Schedule: Letterman Army Hospital - Group I: 3 doses, total of 3.0 mg Fraction I antigen (precise regimen not stated). Group II: 3 doses, total of 12.0 mg Fraction I antigen. Revaccination: groups further divided into 3 subgroups to receive 0.2 mg (intracutaneously), 1.0 mg (subcutaneously) or 1.0 mg (intramuscularly). San Quentin Prison - Group III: (1st and 2nd doses) Fraction 1 antigen and typhoid vaccine, (3rd dose) Fraction I antigen, total of 3.0 mg Fraction I antigen. Group IV: (1st dose) Typhoid vaccine only, (2nd and 3rd doses) Fraction I antigen only, total of 2 mg Fraction I antigen. Group V: total of 3.0 mg Fraction I antigen given in three doses intracutaneously. Group VI: Total of 3.0 mg Fraction I antigen with alum in three doses intramuscularly OUTCOMES: - Stated conclusions: The sc administration of 3 mg of FI, either alone or in the reconstituting medium for lyophilized typhoid vaccine, stimulates significant serologic response in approximately two-thirds of those inoculated. The immunity so produced persists for approximately three months. Revaccination with FI at this time raises the mouse protective antibodies in nearly 95% of previously immunized individuals to levels rarely encountered in plague vaccine studies along similar lines. The antigenic FI is, however, an allergen and may cause delayed allergic reactions - Estimates of efficacy: Letterman Army Hospital - 30 days after last dose of initial series only 60% of the volunteers had protective antibodies of significant concentration in their sera. Irrespective of the size of the dose, the immunity reflected in antibody levels is considered inadequate in the light of comparative tests on laboratory animals. Both groups responded effectively to small booster inoculations. In fact, only one man failed to respond. San Quentin Prison - Fraction I antigen in a dose of 3 mg, stimulated protective antibodies in 50-62% of those inoculated. A two-dose inoculation (group IV) was definitely less immunogenic, and in group VI the addition of alum failed to improve the antigen stimulus. Furthermore, im inoculation (group VI) favours rapid absorption and removal of FI, and a significant antibody response was recorded in only one-third of the group. - Estimates of safety: Letterman Army Hospital - Group I: 11/31 had reactions; and 11/31 had severe reactions. Group II: 14/25 had severe reactions. San Quentin Prison - No severe local or systemic reactions out of 67 participants in four groups. NOTES: (Internal validity) - Selection bias: no measures taken to minimise - Information bias: no measures taken to minimise

Study	Reason for exclusion
	- Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: no measures taken to assess - Appropriateness of statistical methods: not relevant - quality of reporting: good REASON(S) FOR EXCLUSION Non-randomised comparison
Meyer 6	METHODS: - Design: Non-randomised comparison - Comparison(s): Compared new Haffkine vaccine; old Haffkine vaccine and Freeze-dried USP vaccine reference number 3 - Outcome(s): Incidence of local and systemic reaction; Indirect hemagglutination titer; MPI - Follow-up duration: 90 days PARTICIPANTS: - Study population: 48 inmates at the Solano Institute for Medical and Psychiatric Research - At risk groups: Not stated - Incidence of plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): New Haffkine vaccine; old Haffkine vaccine; Freeze-dried USP reference vaccine number 3 (Cutter Laboratories) - Route: Intramuscular - Schedule: Haffkine vaccines - 1 ml on day 0 and 0.2 ml on day 60. USP vaccine - 1 ml on day 0 and 0.5 ml on day 60. OUTCOMES: - Stated conclusions: In the standardised mouse protection test, two broth cultures of virulent Y pestis 195/P killed with formalin (the so-called new and old Haffkine vaccines), examined independently in two laboratories, were proven to have the same protective efficacy. However, accurate assessment of the serologic response to these vaccines (in particular, the MPI values after primary and booster inoculations in men not previously vaccinated) suggests that the new vaccine may be superior to the old in antigenicity. The freeze-dried USP vaccine as a booster antigen stimulated significant MPI in previously vaccinated humans. In all but two of those not previously inoculated, the response was modest. As a result of the above studies, it is possible to venture the opinion that the new type of Haffkine plague vaccine is a superior plague vaccine in terms of antigenicity in man. Vaccinations performed according to current recommendations are well tolerated and induce the appearance of significant levels of antibody in most subjects - Estimates of efficacy: Indirect HA antibody was detected in the sera of all subjects vaccinated with the old or the new type of Haffkine vaccine. Old Haffkine vaccine: MPI of significance appeared in 3/12 on day 30 and 3/13 on day 90. New Haffkine vaccine: MPI of significance appeared in 4/9 on day 30 and 5/9 on day 90. - Estimates of safety NOTES: (Internal validity) - Selection bias: no measures taken to minimise - Information bias: no measures taken to minimise - Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: no measures taken to assess - Appropriateness of statistical methods; not relevant - quality of reporting: good REASON(S) FOR EXCLUSION Non-randomised comparison
Otten 1	METHODS: - Design: Non-randomised population study

Study	Reason for exclusion
	- Comparison(s): None - Outcome(s): Mortality - Follow-up duration: 5 months PARTICIPANTS: - Study population: Inhabitants of two districts in the East Indies (1933-34) - At risk groups: Not stated - Incidence of plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): Haffkine vaccine - Route: Subcutaneous - Schedule: Not stated OUTCOMES: - Stated conclusions: The total number of deaths from bubonic plague ascertained in the 21 weeks amounted to 251, of which 38 occurred in vaccinated and 213 in the control group, giving a mortality rate of 1.01 against 4.75 per mille or a reduction of mortality in vaccinated to almost 20 per cent. - Estimates of efficacy - Estimates of safety NOTES: (Internal validity) - Selection bias: no measures taken to minimise - Information bias: no measures taken to minimise - Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: no measures taken to assess - Appropriateness of statistical methods: not relevant - quality of reporting: good REASON(S) FOR EXCLUSION Non-randomised, non-comparative population study
Otten 2	METHODS: - Design: prospective controlled cohort study and longitudinal observation of mortality - Comparison(s): vaccinated and unvaccinated cohorts - Outcome(s): mortality - Follow-up duration: 6 years PARTICIPANTS: - Study population: two communities in Java (37,000 people in all) in 1935-37 and other populations in Java 1935-1940 - At risk groups: communities in the midst of an epidemic of pneumonic plague - Incidence of plague in study population: not stated INTERVENTIONS: - Type of vaccine(s): Tjiwidej attenuated strain - Route: subcutaneous - Schedule: not stated OUTCOMES: - Stated conclusions: vaccine highly effective in reducing mortality (50-75%) as judged by longitudinal study of mortality (1935-40) - Estimates of efficacy: as above - Estimates of safety: not stated NOTES: (Internal validity) - Selection bias: not addressed - Information bias: not addressed

Study	Reason for exclusion
	- Confounding: not addressed (External validity) - Inference from study to whole population - Precision: not addressed - Appropriateness of statistical methods: not addressed - quality of reporting: good REASON(S) FOR EXCLUSION Non-randomised study.
Reisman	METHODS: - Design: Retrospective assessment of incidences of side-effects following plague vaccine - Comparison(s): None - Outcome(s): Side-effects - Follow-up duration: Patients observed over an 18 month period PARTICIPANTS: - Study population: Military personnel, total 22 healthy adults (19 men, 3 women) - At risk groups: Military personnel assigned to Southeast Asia - Incidence of plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): Killed plague vaccine - Route: Not stated - Schedule: 0 (1 ml), 3 months (0.2 ml). Further doses of 0.2 ml are given every six months to those personnel assigned to Southeast Asia OUTCOMES: - Stated conclusions: The actual incidence of allergic-type reactions from plague vaccine can only be said to be very low - Estimates of efficacy: Not stated - Estimates of safety: 20/22 had immediate urticaria which responded to treatment. 1/22 had an anaphylactic-type reaction consisting of tachycardia, chest tightness and hypertension NOTES: (Internal validity) - Selection bias: no measures taken to minimise - Information bias: no measures taken to minimise - Confounding: no measures taken to minimise (External validity) - Inference from study to whole population - Precision: no measures taken to assess - Appropriateness of statistical methods: not relevant - quality of reporting: good REASON(S) FOR EXCLUSION Retrospective, non-randomised, non-comparative study of the incidences of side- effects in military personnel. A precise rate of incidence could not be given because the total number of doses given was not known.
Vorob'ev	METHODS: - Design: Non-randomised, non-comparative study - Comparison(s): None - Outcome(s): Side-effects; Efficacy - Follow-up duration: One month PARTICIPANTS: - Study population: 4582 people - At risk groups: Not stated - Incidence of plague in study population: Not stated INTERVENTIONS: - Type of vaccine(s): Oral plague vaccine

Study	Reason for exclusion
	- Route: Oral - Schedule: One tablet OUTCOMES: - Stated conclusions: Oral immunisation of people with live plague tablet vaccine is harmless, moderately reactogenic and immunologically efficacious - Estimates of efficacy: Haemagglutinating antibodies could be detected one month after immunisation in 78.8% - Estimates of safety: The overall number of reactions due to the first application of the vaccine constituted 5.2%. In the context of repeat administration of the vaccine, this number was lower at 0.7%. NOTES: (Internal validity) - Selection bias: issue not addressed - Information bias: issue not addressed - Confounding: issue not addressed (External validity) - Inference from study to whole population - Precision: issue not addressed - Appropriateness of statistical methods: issue not addressed - Quality of reporting: Average REASON(S) FOR EXCLUSION Non-randomised, non-comparative study

Characteristics of studies awaiting assessment *[ordered by study ID]*

Pittman

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	—

Characteristics of ongoing studies *[ordered by study ID]*

Greer

Trial name or title	—
Methods	—
Participants	—
Interventions	—
Outcomes	—
Starting date	—

Greer *(Continued)*

Contact information	—
Notes	—

WHAT'S NEW

Date	Event	Description
1 December 2011	New search has been performed	New search conducted September 2011; no new studies identified.

HISTORY

Protocol first published: Issue 1, 1998
Review first published: Issue 1, 1998

Date	Event	Description
23 February 2009	New search has been performed	Search updated. No new studies found
8 October 2008	Amended	Converted to new review format with minor editing.
31 March 2006	New search has been performed	New studies sought but none found.

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- Ministry of Defence, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Plague [immunology] [*prevention & control]; Plague Vaccine [*therapeutic use]; Vaccines, Attenuated [therapeutic use]; Vaccines, Inactivated [therapeutic use]

MeSH check words

Humans